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Evaluation of survival outcomes and prognostic factors in acinic cell carcinomas of the parotid gland receiving adjuvant radiotherapy

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ABSTRACT

Aim: To evaluate the survival outcomes and prognostic factors in acinic cell carcinoma of the parotid gland, a retrospective study was designed.

Material and Method: Consecutive patients diagnosed with parotid acinic cell carcinoma and treated with surgery and adjuvant radiotherapy were retrospectively reviewed. Data regarding age, sex, TNM stage, pathologic characteristics, treatment details, and follow-up examinations were collected and analysed. The primary end-point was overall survival; the distant metastasis free survival was calculated from the date of surgery to the date of death or the latest follow-up examination and analysed by the Kaplan-Meier method. Independent prognostic factors were evaluated by the Cox proportional hazards method.

Results: Between years of 2010-2020, two radiotherapy centers' database were reviewed. A total of 32 patients were included. The median age was 55 years (35-80 years). Four-teen (43.75%) were male and 18 (56.25%) were female. Median follow-up was 44 months (8-120). Seven (21.9%) were in T1, 7 (21.9%) in T2, 6 (18.8%) in T3 and 12 (37.5%) in T4 at the time of diagnosis. In all cohort, 6 (18.8%) of them had lymph node metastasis. The 2-year and 5-year OS rates were 92.6% and 78.5%, locoregional recurrence-free survival rates were 100% and 89.1%, distant metastasis free survival rates were 85.9% and 85.9%, respectively. Locoregional recurrence detected in 2 (6.25%), distant metastases detected in 4 (12.5%) patients. All distant metastases detected in the lungs. Univariate analysis showed that age, gender, margin status, T stage, facial nerve involvement, lymphovascular invasion, and perineural invasion were not significantly related to overall survival (all $p>0.05$). Lymph node involvement ($p<0.013$) and grade ($p<0.006$) were the only significant prognostic factors for OS. In multivariate analysis, both lymph node involvement ($p<0.050$) and grade ($p<0.028$) remained the significant prognostic factors.

Conclusion: In acinic cell carcinoma of the parotid gland, high-grade histology and node positivity are independent variables that affect OS. Since survival is lower in these patient groups, it is imperative to explore other treatment options in addition to adjuvant radiotherapy.

Keywords: Parotid cancer, acinic cell carcinoma, prognostic factors, radiotherapy, survival

INTRODUCTION

Acinic cell carcinoma (ACCs) is a very rare malignant tumor. The vast majority are located in the parotid gland (86% of cases) (1) and constitute 6-16% of all malignant tumors originating from the major salivary glands (2). It was defined as benign adenoma by Goodwin et al. (3) in 1890, recognized as a malignant tumor by Buxton et al. (4) in 1953 and is currently classified as malignant by World Health Organization (5). Although it's been considered for a long period of time a neoplasm with a good prognosis, currently, we should take into account it as a malignancy with an uncertain clinical course, since this tumor tends to recur, metastasize, and even cause death, particularly for a subgroup, defined as "ACCs with high-grade transformation".

The prognostic factors in ACCs are not well documented, due to the small sample size, poor quality of medical records, and difficulty in organizing randomized trials. In this study, we retrospectively evaluated survival outcomes and prognostic factors in parotid ACCs who received surgery and adjuvant radiotherapy (RT). Medical records of two RT centers were collected for increasing the sample size.

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MATERIAL AND METHOD

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by a local human research committee. The study protocol was reviewed and approved by the Clinical Research Ethics Committee (Date: 12/04/2022, Decision No: 2022/176). Written informed consent forms were read by each patient and signed consent was obtained prior to their treatment. Medical records of two RT centers were reviewed. Between January 2010 and January 2020, a total of 32 cases with ACCs, who met with the inclusion criteria, included in the study.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Who diagnosed with ACCs in parotid gland,
- Patients were> 18 years of age
- Who underwent a currative surgery,
- Who received adjuvant RT,
- Cases without a postoperative macroscopic residual mass,
- Cases who have not received neoadjuvant, adjuvant or concurrent chemotherapy

Exclusion criteria:

- Relapsed disease prior to adjuvant RT,
- Cases with no surgery for curative intent,
- Cases with a previous history of another malignant disease,
- Who developed a second primary malignancy during followup period,
- Cases with metastases prior to RT,
- Cases with postoperative macroscopic residual mass (R2 resection),
- Cases with immunosuppressive disease.

Statistical Analysis

Study data were analyzed using the statistical package program Statistical Package for the Social Sciences version 25.1 (SPSS, Inc., Chicago, IL, ABD). Numeric, percentage, standard deviation, mean, minimum and maximum values were used as descriptive statistics. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) were estimated using the Kaplan-Meier method. To identify prognostic factors that might affect survival, log rank tests were performed to examine univariate relationships between survival and parameters of interest, and Cox regression analysis to examine multivariate relationships. A value of $p<0.05$ was considered statistically significant.

RESULTS

Patient and Histopathological Characteristics and Treatment Outcomes

We analyzed overall outcomes and investigated potential prognostic variables such as age, gender, T stage and N stage, facial weakness, histologic grade, extraglandular spread, resection margins, perineural invasion and lymphovascular invasion. The date of diagnosis was accepted as the histological diagnosis date. The last follow-up date was the last consultation date. All tumors were classified by the tumor (T), lymph node (N), and metastasis staging system, seventh edition (International Union Against Cancer, 2009). Of 32 patients, all were located in parotid glands. The median age was 55 years (35-80 years). Four-teen (43.75%) were male and 18 (56.25%) were female. Median follow-up was 44 months (8-120). Seven (21.9%) were in T1, 7 (21.9%) in T2, 6 (18.8%) in T3 and 12 (37.5%) in T4 at the time of diagnosis. In all cohort, 6 (18.8%) of them had lymph node metastasis. (**Table 1**) During the analysis, T1 and T2, T3 and T4 were placed together in two groups, and lymph node status were divided into two groups according to the presence of metastasis or not. T4A and T4B tumours were grouped together as T4. Twenty-one (65.6%) patients had free of surgical margins, and 9 (28.12%) positive margins, data of 2 (6.25%) cases missed. Grade was recorded in all patients. They were divided into two groups as being either low-grade (23 cases), including well and moderately differentiated tumors, or high-grade (9 cases), including poorly differentiated or undifferentiated tumors. For perineural invasion (PNI), 9 (28.1%) were positive, 13 (40.6%) were negative and 10 (31.3%) were missed. For lymphovascular invasion (LVI), 7 (21.9%) were positive, 20 (62.5%) were negative and 5 (15.6%) were missed. Four (12.5%) patients had facial paralysis at the time of first admission. All patients underwent a curative surgery. Among the whole cohort, 12 (37.5%) underwent total parotidectomy alone, 10 (31.25%) superficial parotidectomy, 10 (31.25%) total parotidectomy with neck dissection. Of these neck dissected 10 cases, 6 (18.75%) of theme underwent therapeutic and 4 (12.5%) elective dissection. Node involvement was present in 6 (18.75%) cases. Only patients who underwent definitive PORT were included in the study. For the cohort, RT indications were as follows: patients with T3-T4 tumor, and/or lymph node positivity, and/or perineural, and/or lymphovascular invasion, and/or positive surgical margins, and/or high-grade tumor, and/or extraglandular spread were considered high-risk patients and had one or more of these features were treated by RT. The median duration of RT was 44 days (range 39-52). For 18 (56.25%) patients, RT was applied only to the postoperative tumor bed, and for 14 (43.75%) patients, the neck region was also included in the RT treatment area. An average of 50 Gy (46-66 Gy) delivered to the neck region and 60 Gy (50-70 Gy) for the tumor bed.

Table 1. Demographic and pathologic features

Baseline characteristic	Total No. patients	Percent
Gender		
Female	18	56.2%
Male	14	43.7%
Grade		
Low-grade (1 or 2)	23	71.8%
High-grade (3 or 4)	9	28.1%
T stage		
T1or T2	14	43.7%
T3 or T4	18	56.2%
Lymph node status		
N0	26	81.2%
N+	6	18.8%
Margin		
Negative	21	65.6%
Positive	9	28.1%
Missed	2	6.2%
Perineural invasion		
Invasion –	13	40.6%
Invasion +	9	28.1%
Missed	10	31.3%
Lymphovascular invasion		
Invasion –	20	62.5%
Invasion +	7	21.9%
Missed	5	15.6%

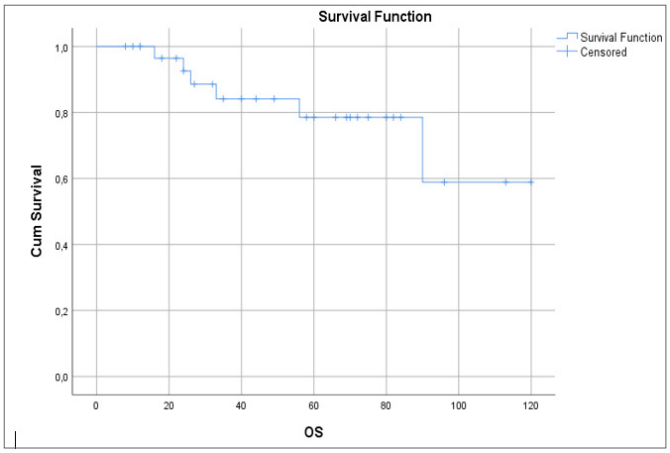
No patients received a chemotherapy for curative intent. First doctor visits were made 4-6 weeks after the end of treatments. Than, patients were followed-up every 3 months for 2 years, and every 6 months thereafter. Physical examination routinely performed for each single patients. Head-neck/thorax computed tomography scan was performed during the follow-up period, if necessary.

Survival Outcomes and Prognostic Factors

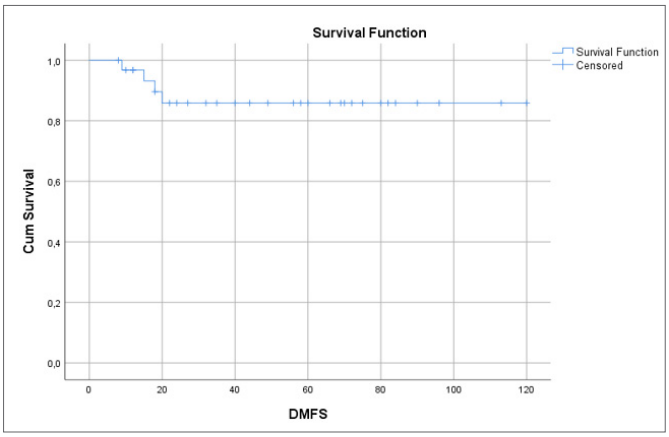
The 2-year and 5-year OS rates were 92.6% and 78.5% (**Graphic 1**), LRFS rates were 100% and 89.1%, DMFS rates were 85.9% and 85.9% (**Graphic 2**), respectively. Locoregional recurrence detected in 2 (6.25%), distant metastases detected in 4 (12.5%) patients. All distant metastases detected in the lungs. Locoregionally recurred patients both recurred locally, there was no regional recurrence in this cohort.

Univariate analysis showed that age, gender, margin status, T stage, facial nerve involvement, lymphovascular invasion, and perineural invasion were not significantly related to OS (all $p > 0.05$). Lymph node involvement ($p<0.013$) and grade ($p<0.006$) were the only significant prognostic factors for OS. In multivariate analysis, both lymph node involvement ($p<0.050$) and grade ($p<0.028$) remained the significant prognostic factors.

Univariate analysis revealed that gender ($p<0.018$) and lymph node involvement ($p<0.001$) were the only significant prognostic factors for LRFS. In multivariate analysis, neither were significant prognostic factors.



Graphic 1. Overall Survival curve



Graphic 2. Distant Metastases Free Survival curve

Univariate analysis revealed that grade ($p<0.001$) were the only significant prognostic factor for DMFS. Thus, multivariate analysis was not performed.

DISCUSSION

In most series, parotid gland ACCs were detected more in women than in men (6). Duzova et al. (7) reported a female dominancy for ACCs histology. Similarly, in the presented cohort, females (56.25%) are more affected than males (43.75%). This tumor affect a wide age range, from younger to older people. It can even be detected in pediatric age groups (8). Most ACCs appear between the ages of 40-49 years (6). In our cohort, age ranged from 35 to 80 years and most of theme were in fourth (34.37%) and fifth (34.37%) decades.

Efforts related to histological grading have not reached a definitive conclusion and are still a controversial issue. Features often associated with more aggressive tumors include frequent mitosis, focal necrosis, neural invasion, pleomorphism, infiltration, and stromal hyalinization. In ACCs, cases of from low- to high-grade de-differentiation have been reported. These cancers are defined with cytological pleomorphism, accrued proliferative and mitotic activity, proliferation indices and having a poor prognosis (9). Currently, It is reported

that up to 35% of ACCs, which were wrongly thought to be a benign tumor in the past, are high-grade. This topic is too important, predictably, since high-grade ACCs are related with advanced disease, a higher incidence of recurrence, distant metastasis, and worse prognosis (10). In the present study, high-grade tumor associated with poorer OS both for univariate and multivariate analysis and it seemed to be related with distant metastasis. In a retrospective study by Fang et al. (11) analyzed the medical records of 144 patients and they reported high-grade and intraparotid lymph node positivity as an indepent prognosticators in patients with ACCs histology. In this study, female gender (57.6%) was dominant and the mean age of the study population was 54.8 years as similar to our study. High mitotic rate, high-grade transformation, close and involved surgical margins, and necrosis were negative prognosticators, according to the results of a recently reported Dutch study of 89 ACCs cases treated and retrospectively reviewed between 1979 and 2016. In conclusion, they suggested that due to the relatively high incidence of high-grade transformation (21%) in ACCs and the low accuracy of cytology, elective neck dissection may be considered as part of standard treatment (12).

Various studies have previously examined the rate of lymph node metastasis in major salivary gland acinar cell carcinoma and have reported varying results. In a retrospective review of 66 patients from four different institutions examining nodal metastases in acinar cell carcinoma of the parotid gland, a metastasis rate of 34.3% was found in cases with neck dissection, and the overall incidence for the entire group of 66 diseases was 18.2% (13). A relatively small retrospective study from a single institution examined 14 cases and showed a 9% lymph node metastasis rate (14). Nodal metastases of ACCs reported in the literature ranges from 0% to 43%; The rate of occult regional metastases ranges from 0% to 13% (15). In the present study, lymph node involvement was present in 6 (18.75%) cases. This rate was relatively high in the current study, as the population of our study consisted of patients receiving RT, and patients who were candidates for RT were high-risk patients. Additionally, local recurrence developed in 2 patients. Remarkably, both of these two patients consisted of T4 and node positive patients. Lymph node positivity was found to be a prognostic factor affecting both survival and recurrence. Similiarly, in a large retrospective study of 255 patients with major salivary gland carcinomas in Brazil, clinical stage, positive lymph nodes, facial palsy, and invasion of adjacent structures were found to be predictors of distant metastases (16).

Margin status appears to play an important role in survival in AciCC patients. Clear margin is a positive prognostic factor for survival (12). In a retrospective case series with medical record review, patients treated surgically between the years from 2000 to 2014 for ACCs of the parotid gland were identified from an institutional database and 45 patients were included for analysis. They aimed to evaluate the effect of RT, particularly in patients with negative but close margins (≤1 mm) and no other high-risk histopathological factors. In conclusion, they stated that RT was unnecessary in patients with ACCs of the parotid gland with close (≤1 mm) but negative surgical margins and no other high risk factors (17).

Unlike many studies, in our cohort, perineural invasion and lymphovascular invasion are not rare features in ACCs, with an incidence of 28.1% and 21.9%, respectively. However, similar higher incidences were reported by Gomez et al. (23% vs 8.6%) (18). Despite this relatively low incidence of both features, their presence adversely affects survival, as in other salivary gland carcinomas (18,19). In the current study, neither perineural invasion nor lymphovascular invasion was a negative prognosticator (OS, LRFS and DMFS $p > 0.05$).

Surgery remains the mainstay of treatment in parotid gland ACCs. The necessity of adjuvant RT to whom in this patient group is still a controversial issue today. Although disease recurrences or distant metastases may be seen in some patients with parotid gland ACCs, most of the population with this disease has a more benign course and can be cured mostly with surgical treatment alone. Spafford et al. (20) reported recommendations regarding with adjuvant RT in ACCs in 1991. They recommended RT as an adjuvant treatment in addition to surgery in patients with the following features: recurrent disease, suspicious or surgical margins positivity, tumor adjacent to the facial nerve or facial nerve involvement, deep lobe involvement, lymph node metastases, extraglandular extension and tumors size greater than 4 cm. In a retrospective study published in 2018, Zenga et al. (17). aimed to illuminate a confusing issue. As we mentioned above, they questioned the role of RT in patients with ACCs with close (≤1 mm) surgical margins who had no other high risk factors and stated that RT was unnecessary in this group of patients. In another retrospective study published in 2018, Greig et al. (21) recommended adjuvant RT in high-grade tumors and in cases of surgical margin proximity or positivity. If we need to emphasize in line with the results of our study, there is a need for additional treatment options to adjuvant RT because the survival rate is lower in those with high grade and node positivity. Recent advances in drug studies have led to major changes in many treatment guidelines. In the era of immunotherapy, it is hoped that in the near future, drugs that will positively affect the prognosis in these tumor subgroups will be on the agenda.

The limitations of the present study should be acknowledged. First, there is an inherent bias in retrospective studies. Second, the sample size was relatively small, possibly reducing statistical power; Third, the entire patient population consisted of relatively high-risk patients undergoing adjuvant RT; therefore, studies with larger sample sizes are needed to confirm the results.

CONCLUSION

In ACCs of the parotid gland, high-grade histology and node positivity are independent variables that affect OS. Because survival is lower in these patient groups, it is imperative to explore other treatment options in addition to adjuvant RT. Multicenter, randomized studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was reviewed and approved by the Clinical Research Ethics Committee (Date: 12/04/2022, Decision No: 2022/176).

Informed Consent: Written informed consents of all patients were acquired prior to treatment.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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